



B/TFW  
1618

PATENT

Attorney Docket No. 12971US04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Grant L. Schoenhard

Serial No.: 10/000,113

Filing Date: October 30, 2001

For: Inhibitors of ABC Drug Transporters at  
the Blood-Brain Barrier

Examiner: Vickie Y. Kim

Group Art Unit No.: 1618

Confirmation No.: 8969

Customer No.: 23446

**Certificate of Delivery by Hand**

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Victoria Messenger

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

This Supplemental Information Disclosure Statement ("Supplemental IDS") and the references cited herein are being hand delivered on September 29, 2005. A courtesy copy of this Supplemental IDS, along with a copy of each of the following cited reference, is being hand delivered to the Examiner on the same date:

1. Zhen-Li Liu, et al., "Persistent reversal of P-glycoprotein-mediated daunorubicin resistance by tetrandrine in multidrug-resistant human T lymphoblastoid leukemia MOLT-4 cells," *Journal of Pharmacy and Pharmacology*, 55:1531-1537 (2003).
2. Hiroyuki Kusuvara, et al., "Role of transporters in the tissue-selective distribution and elimination of drugs: transporters in the liver, small intestine, brain and kidney," *Journal of Controlled Release*, 78:43-54 (2002).

3. Editorial, "Membrane Transporters," *European Journal of Pharmaceutical Sciences*, 21:1 (2004).
4. Haiying Sun, et al. "Drug efflux transporters in the CNS," *Advanced Drug Delivery Reviews*, 55:83-105 (2003).
5. Richard B. Kim, "Pharmacogenetics of CYP enzymes and drug transporters:remarkable recent advances," *Advanced Drug Delivery Reviews*, 54:1241-1242 (2002).
6. Tetsuya Terasaki, et al., "The blood-brain barrier efflux transporters as a detoxifying system for the brain," *Advanced Drug Delivery Reviews*, 36:195-209 (1999).
7. Akira Tsuji, et al., "Carrier-mediated or specialized transport of drugs across the blood-brain barrier," *Advanced Drug Delivery Reviews*, 36:277-290 (1999).
8. Massimo Rizzi, et al., "Limbic Seizures Induce P-Glycoprotein in Rodent Brain: Functional Implications for Pharmacoresistance," *The Journal of Neuroscience*, 22(14):5833-5839 (July 15, 2002).
9. Astrid A. Ruefli, et al., "HMBA induces activation of a caspase-independent cell death pathway to overcome P-glycoprotein-mediated multidrug resistance," *Blood*, Vol. 95, No. 7, 2378-2385 (April 1, 2000).
10. Mark J. Smyth, et al., "The drug efflux protein, P-glycoprotein, additionally protects drug-resistant tumor cells from multiple forms of caspase-dependent apoptosis," *Proc. Natl. Acad. Sci. USA*, Vol. 95:7024-7029 (June 1998).
11. Miki Susanto, et al., "Can the Enhanced Renal Clearance of Antibodies in Cystic Fibrosis Patients be Explained by P-Glycoprotein Transport?," *Pharmaceutical Research*, Vol. 19, No. 4, 457-462 (April, 2002).
12. Seong Hoon Jang, et al., "Kinetics of P-Glycoprotein-Mediated Efflux of Paclitaxel," *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 298, No. 3, 1236-1242 (2001).
13. Ricky W. Johnstone, et al., "A Role for P-Glycoprotein in Regulating Cell Death," *Leukemia and Lymphoma*, Vol. 38 (1-2), 1-11 (2000).
14. Ricky W. Johnstone, et al., "P-Glycoprotein Does Not Protect Cells against Cytolysis Induced by Pore-forming Proteins," *The Journal of Biological Chemistry*, Vol. 276, No. 20, 16667-16673 (May 18, 2001).

15. Ricky W. Johnstone, et al., "P-Glycoprotein Protects Leukemia Cells Against Caspase-Dependent, but not Caspase-Independent, Cell Death," *Blood*, Vol. 93, No. 3, 1075-1085 (February 1, 1999).
16. Richard B. Kim, "Drugs As P-Glycoprotein Substrates, Inhibitors, and Inducers," *Drug Metabolism Reviews*, 34(1&2), 47-54 (2002).
17. Pamela L. Golden, et al., "Brain Microvascular P-Glycoprotein and a Revised Model of Multidrug Resistance in Brain," *Cellular and Molecular Neurobiology*, Vol. 20, No. 2, 165-181 (2000).
18. Hirofumi Hamada, et al., "Characterization of the ATPase Activity of the M<sub>r</sub> 170,000 to 180,000 Membrane Glycoprotein (P-Glycoprotein) Associated with Multidrug Resistance in K562/ADM Cells," *Cancer Research*, 48:4926-4932 (September 1, 1988).
19. Donna S. Cox, et al., "Influence of multidrug resistance (MDR) proteins at the blood-brain barrier on the transporter distribution of enaminone anticonvulsants," *J. Pharm. Sci.*, Vol. 90, No. 10, pages 1540-1552 (2001)
20. A. H. Dantzig, et al., "Considerations in the design and development of transport inhibitors as adjuncts to drug," *Advanced Drug Delivery Reviews*, Vol. 55, No. 1, pages 133-150 (2003).
21. A. H. Dantzig, et al., "Evaluation of the binding of the tricyclic isoxazole photoaffinity label LY475776 to multidrug resistance associated protein 1 (mrp1) orthologs and several ATP-binding cassette (ABC transporters)," *Biochemical Pharmacology*, Vol. 67, No. 6, pages 1111-1121 (2004)
22. T.R. Slouch, "Progress in understanding the structure-activity relationships of p-glycoprotein," *Advanced Drug Delivery Reviews*, Vol. 54, No. 3, pp. 315-328 (2002)
23. A.H. Schinkel, "Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview," *Advanced Drug Delivery Reviews*, Vol. 55, No. 1, pp. 3-29 (2003)
24. Pamela L. Golden, et al., "Blood-Brain Barrier Efflux Transport," *Journal of Pharmaceutical Sciences*, Vol. 92, No. 9, 1739-1753 (September 2003).

In compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98, this Supplemental IDS, the attached Form PTO/SB/08A, and a copy of the document cited therein is submitted for consideration in connection with the above-

identified patent application. It is respectfully requested that the Examiner indicate on attached Form PTO/SB/08A that the cited document has been considered.

This statement should not be construed as a representation that an exhaustive search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This Supplemental Information Disclosure Statement is being submitted before receipt of a first Office Action in the above-identified application, thus Applicants believe no fee is due. Nonetheless, the U.S. Patent and Trademark Office is hereby authorized to charge any required fee, or credit any overpayment, to our Deposit Account No. 13-0017 in the name of McAndrews, Held & Malloy, Ltd.

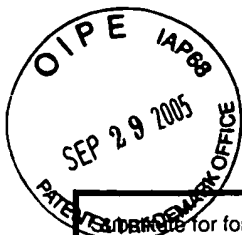
Respectfully submitted,

Dated: September 29, 2005

A handwritten signature in black ink, reading "Michael B. Harlin", written over a horizontal line.

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PTO/SB/08A (08-03)

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Information Disclosure Statement by Applicant				Complete if Known		
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)				Application Number	10/000,113	
				Filing Date	October 30, 2001	
				First Named Inventor	Grant L. Schoenhart	
				Group Art Unit	1618	
				Examiner Name	Vickie Y. Kim	
Sheet 1 of 2				Attorney Docket Number	12971US04	
<b>U.S. PATENT DOCUMENTS</b>						
Examiner Initial*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	
	A					
<b>FOREIGN PATENT DOCUMENTS</b>						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
	B					
<b>OTHER ART -- NON PATENT LITERATURE DOCUMENTS</b>						
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published				
	C1	Zhen-Li Liu, et al., "Persistent reversal of P-glycoprotein-mediated daunorubicin resistance by tetrandrine in multidrug-resistant human T lymphoblastoid leukemia MOLT-4 cells," <i>Journal of Pharmacy and Pharmacology</i> , 55:1531-1537 (2003).				
	C2	Hiroyuki Kusuvara, et al., "Role of transporters in the tissue-selective distribution and elimination of drugs: transporters in the liver, small intestine, brain and kidney," <i>Journal of Controlled Release</i> , 78:43-54 (2002).				
	C3	Editorial, "Membrane Transporters," <i>European Journal of Pharmaceutical Sciences</i> , 21:1 (2004).				
	C4	Haiying Sun, et al. "Drug efflux transporters in the CNS," <i>Advanced Drug Delivery Reviews</i> , 55:83-105 (2003).				
	C5	Richard B. Kim, "Pharmacogenetics of CYP enzymes and drug transporters: remarkable recent advances," <i>Advanced Drug Delivery Reviews</i> , 54:1241-1242 (2002).				
	C6	Tetsuya Terasaki, et al., "The blood-brain barrier efflux transporters as a detoxifying system for the brain," <i>Advanced Drug Delivery Reviews</i> , 36:195-209 (1999).				
	C7	Akira Tsuji, et al., "Carrier-mediated or specialized transport of drugs across the blood-brain barrier," <i>Advanced Drug Delivery Reviews</i> , 36:277-290 (1999).				
	C8	Massimo Rizzi, et al., "Limbic Seizures Induce P-Glycoprotein in Rodent Brain: Functional Implications for Pharmacoresistance," <i>The Journal of Neuroscience</i> , 22(14):5833-5839 (July 15, 2002).				
	C9	Astrid A. Ruefli, et al., "HMBA induces activation of a caspase-independent cell death pathway to overcome P-glycoprotein-mediated multidrug resistance," <i>Blood</i> , Vol. 95, No. 7, 2378-2385 (April 1, 2000).				
	C10	Mark J. Smyth, et al., "The drug efflux protein, P-glycoprotein, additionally protects drug-resistant tumor cells from multiple forms of caspase-dependent apoptosis," <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 95:7024-7029 (June 1998).				
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EXAMINER SIGNATURE		DATE CONSIDERED				

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup>Kind of document by the appropriate symbols as indicated on the document under WIPO Standard St. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450 Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. Send TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Substitute for form 1449A/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		<b>Complete if Known</b>	
		Application Number	10/000,113
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		First Named Inventor	Grant L. Schoenhard
		Group Art Unit	1618
		Examiner Name	Vickie Y. Kim
Sheet	2	Of	2
		Attorney Docket Number	12971US04

## U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C12	Seong Hoon Jang, et al., "Kinetics of P-Glycoprotein-Mediated Efflux of Paclitaxel," <i>The Journal of Pharmacology and Experimental Therapeutics</i> , Vol. 298, No. 3, 1236-1242 (2001).			
	C13	Ricky W. Johnstone, et al., "A Role for P-Glycoprotein in Regulating Cell Death," <i>Leukemia and Lymphoma</i> , Vol. 38(1-2), 1-11 (2000).			
	C14	Ricky W. Johnstone, et al., "P-Glycoprotein Does Not Protect Cells against Cytolysis Induced by Pore-forming Proteins," <i>The Journal of Biological Chemistry</i> , Vol. 276, No. 20, 16667-16673 (May 18, 2001).			
	C15	Ricky W. Johnstone, et al., "P-Glycoprotein Protects Leukemia Cells Against Caspase-Dependent, but not Caspase-Independent, Cell Death," <i>Blood</i> , Vol. 93, No. 3, 1075-1085 (February 1, 1999).			
	C16	Richard B. Kim, "Drugs As P-Glycoprotein Substrates, Inhibitors, and Inducers," <i>Drug Metabolism Reviews</i> , 34(1&2), 47-54 (2002).			
	C17	Pamela L. Golden, et al., "Brain Microvascular P-Glycoprotein and a Revised Model of Multidrug Resistance in Brain," <i>Cellular and Molecular Neurobiology</i> , Vol. 20, No. 2, 165-181 (2000).			
	C18	Hirofumi Hamada, et al., "Characterization of the ATPase Activity of the M <sub>r</sub> 170,000 to 180,000 Membrane Glycoprotein (P-Glycoprotein) Associated with Multidrug Resistance in K562/ADM Cells," <i>Cancer Research</i> , 48:4926-4932 (September 1, 1988).			
	C19	Donna S. Cox, et al., "Influence of multidrug resistance (MDR) proteins at the blood-brain barrier on the transporter distribution of enaminone anticonvulsants," <i>J. Pharm. Sci.</i> , Vol. 90, No. 10, pages 1540-1552 (2001).			
	C20	A. H. Dantzig, et al., "Considerations in the design and development of transport inhibitors as adjuncts to drug," <i>Advanced Drug Delivery Reviews</i> , Vol. 55, No. 1, pages 133-150 (2003).			
	C21	A. H. Dantzig, et al., "Evaluation of the binding of the tricyclic isoxazole photoaffinity label LY475776 to multidrug resistance associated protein 1 (mrp1) orthologs and several ATP-binding cassette (ABC transporters)," <i>Biochemical Pharmacology</i> , Vol. 67, No. 6, pages 1111-1121 (2004).			
	C22	T.R. Slouch, "Progress in understanding the structure-activity relationships of p-glycoprotein," <i>Advanced Drug Delivery Reviews</i> , Vol. 54, No. 3, pp. 315-328 (2002).			
	C23	A.H. Schinkel, "Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview," <i>Advanced Drug Delivery Reviews</i> , Vol. 55, No. 1, pp. 3-29 (2003).			
	C24	Pamela L. Golden, et al., "Blood-Brain Barrier Efflux Transport," <i>Journal of Pharmaceutical Sciences</i> , Vol. 92, No. 9, 1739-1753 (September 2003).			

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